HEPATITIS AND ITS RELATION TO CHOLECYSTITIS

By Walton Martin, M.D.

of New York, N. Y.

THE MUTTER LECTURE DELIVERED BEFORE THE PHILADELPHIA COLLEGE OF PHYSICIANS, DECEMBER 10, 1926

In several papers written during the last nine years, Evarts Graham,[1, 2, 3] whom I think your Committee honored the year before last as it has me this year, has presented some interesting observations and stimulating suggestions on the pathogenesis of hepatitis and cholecystitis, on the path of infection in diseases of the gall-bladder and on the association of cholecystitis and hepatitis.

In reading these papers and others on the same subject, I am reminded of a saying of the hæmatologist Naegeli, quoted by Aschoff.[4] He writes: "It is a sure sign of the undeveloped state of science if the logical concepts with which it deals are not fixed and when multiple meanings are assigned to the same term." I am reminded of this saying because of the confusion in my own mind regarding the exact meaning of hepatitis and cholecystitis. Perhaps the disagreement and controversies that arise between clinical surgeons, pathologists and physicians, when terms such as hepatitis and cholecystitis are used, are inevitable in the uncertain state of much of our knowledge regarding these subjects and the different conceptions formed when these terms are used.

At the outset it may be well to refer briefly to the observations that have been made regarding hepatitis and cholecystitis by a number of surgeons during the last ten years and to state the conclusions that have been drawn from these observations. Small sections of the liver removed during operations for cholecystitis have regularly shown varying degrees of hepatitis. The lesions are confined largely to the interstitial tissue where the lymphatics are situated. In several instances pieces of liver removed during operations for chronic appendicitis have shown inflammatory changes. Gall-bladders removed for a group of clinical symptoms which are classed as dyspepsia, and in which there was no history of gall-stone colic, have not infrequently shown very slight or no macroscopic lesions, but have shown, under the microscope, slight inflammatory infiltration of the deeper layers of the walls of the gall-bladder. The conclusion has been reached that in many cases of cholecystitis there has been a direct extension to the wall of the gall-bladder from an inflamed liver; that frequently a vicious circle exists between the gall-bladder and the liver whereby each may infect the other; that the infection of the liver from an inflamed gall-bladder is an important factor in the production of cirrhosis; that lesions of the gall-bladder wall that cannot be readily recognized macroscopically give definite clinical symptoms.

I may also add at the outset that anyone having the temerity to discuss hepatitis is thrown on the horns of a dilemma. Either he must discuss the

subject as if hepatitis were a simple entity or he must refer to its very complex and diversified etiology and be carried into a rather loose-jointed and rambling discussion. I must beg your indulgence for the latter method.

I have thought, however, it might be of advantage to bring forward some of the problems that present themselves when the somewhat indefinite word hepatitis is used and to consider the interesting question as to when the reaction of the cells that make up the liver and the gall-bladder reaches the plane of clinical observation. In other words, what degrees of reaction in the hepatic cells or the gall-bladder wall are we justified in considering clinical entities.

There are a few features in the microscopical anatomy and physiology which seem to me pertinent to the discussion. The arrangement and relation of the blood and lymph capillaries to the liver cells are imperfectly understood. There is, however, a fairly general agreement that the portal vein and the hepatic artery spread out into the intricate capillary network which is very intimately related to the liver cells. The Danish zoologist, Krogh,[5] who has made most extensive studies of the anatomy and physiology of the capillaries, considers that the endothelium of the hepatic capillaries is a syncytium with numerous nuclei but without defined cell borders as in the embryonal capillaries, and that the star cells of Von Kupffer, which appear at rather short, regular intervals, are an integral part of the capillary wall. The English histologist, Schafer,[6] believes that what remains of the endothelium of the liver sinuses is represented by these stellate cells.

Blood, entering the liver through the portal vein and hepatic artery, spreads out in a large and complex capillary network, the liver cells being directly bathed by blood and not by lymph, as elsewhere in the body. Besides the polygonal liver cells and the Von Kupffer cells which make up, with the capillaries, the lobules, there is a connective-tissue stroma underneath the serous covering and between the lobules which supports the bile ducts and blood-vessels in their course through the organs. The lymphatic vessels arise from the lymph capillaries in this connective-tissue stroma. Numerous lymph vessels accompany the interlobular branches of the portal vein and numerous lymph vessels accompany the hepatic vein.

From the study of the injection specimens made by Sappey,[7] it seems that a considerable number of fairly large lymph vessels pass along the inferior surface of the liver over the body of the gall-bladder from the adjoining quadrate lobe and the right lobe, to form an extensive anastomosing network of vessels in the neighborhood of the neck of the gall-bladder. Others, derived from the same sources, pass behind the gall-bladder to terminate in the same region. There are apparently numerous anastomosing lymph capillaries between the lymphatics of the liver and the gall-bladder.

The hepatic cells have many and diversified functions. The liver is the great laboratory and storehouse of the body. It is engaged in chemical transformations, demonstrated by the high consumption of oxygen and the production of heat. All three classes of foodstuffs—carbohydrates, fats, and

probably proteins—are built up into large non-diffusible molecules and stored in the liver cells and, by reversible ferments, again changed into soluble forms which pass out into the circulation as needed. The liver cells change the amino acids to simpler compounds, produce bile with its well-known function and play an important part in the coagulation of the blood.

But it is to a function which it shares with the reticulo-endothelial system, in rendering harmless various toxic substances and in the destruction and disposal of living microörganisms and red blood-cells, that I wish to call special attention. The stellate cells of Kupffer, which we have just said are part of the lining endothelium of the liver capillaries, belong to the group of reticulo-endothelial cells which are found in the sinuses and pulp cords of the lymph-nodes, the reticulum and the blood sinuses of the spleen and the capillaries of the bone-marrow. These cells behave in a special way in taking up dyes and other substances and show a pronounced capacity for phagocytosis.

Kupffer showed that the star cells in the liver were loaded with the pigment after the injection of india ink. These experiments have been many times confirmed. Various chemicals injected into the circulation are taken up in the same way by the stellate cells. Certain salts are not arrested; the cells show a power of selection and certain substances are taken up and stored in the liver cells. A number of careful experiments by Roger [8] and others have shown that alkaloids are arrested in the same way in the liver. Some of the alkaloids lose a portion of their toxicity in passing through the liver; some of them are excreted in the bile and, according to Roger and others, the detoxicating effect varies with the abundance of glycogen in the liver.[9] There can be no question of the arrest, storage and destruction in the liver of a number of simple and complex chemical substances.

The action of the liver on microbes is equally interesting. Wyssokowitsch[10] showed, many years ago, that pathogenic and non-pathogenic microbes and the spores of molds were arrested and taken up by the cells of the capillaries and sinuses in the liver, bone-marrow and spleen. The capillaries and sinuses in these regions are great settling basins where all manner of minute foreign substances are deposited and taken up. Although all the cells of the so-called reticulo-endothelial system in these situations are largely concerned in the reactions, it by no means implies that their behavior in the liver, spleen and bone-marrow is the same. The stellate cells of the liver are not the exact equivalent of the endothelial cells of the splenic sinuses, for example. Bacteria are not taken up to the same extent in all the depots of this system of cells. The Kupffer cells of the liver seem to take up and retain large numbers of microbes at an early stage, at least in inoculation with certain microbes and in certain animals.

Bacteria and other foreign substances taken up by the reticulo-endothelial cells in the bone-marrow and spleen are destroyed there or start to grow and invade again the blood stream. But for the material deposited and taken up by the liver cells there is another possibility. The foreign particles may be

excreted in the bile. In Wyssokowitsch's (*l. c.*) experiments he expressly states that the bacteria taken up from the blood stream do not pass out by the excretions and secretions of the body. But it has been proved over and over again, during the last forty years since he made his precise and interesting observations, that bacteria injected into the portal vein or the systemic veins, if injected in sufficient dosage, regularly enter the bile. Nichols [11] recorded in 1916 a number of carefully carried out experiments and reviewed and criticized the work done up to that time by Fütterer, Chiarolanza and Koch. He injected varying doses of typhoid bacilli and cholera vibrios into the systemic veins and into the portal vein in immune animals and in animals in which no immunity had been established. He found fairly large doses were necessary to make bacilli appear in the bile and a larger dosage was required in the systemic veins than in the branches of the portal vein. He records several instances in which the results were strikingly inconstant; the same dosage injected in a portal vein in one instance showing numerous colonies cultured from the bile and in another showing not a single colony. There were marked individual variations in elimination. Immune animals showed a greater power of excreting bacteria in the bile than non-immune animals. Rapid agglutination *in vivo,* deposition in the liver and corresponding elimination are suggested as explanations. The bacilli began to appear in the bile with astonishing rapidity; being found in two to three minutes after portal injection and the first plates showed the largest number of colonies.

The reticulo-endothelial cells are concerned not only in taking up foreign bodies and, through the action of various intracellular ferments, modifying or destroying them, but they are also concerned in furnishing and secreting various substances which aid in the destruction of microörganisms and in the neutralization of their toxins. Metchnikoff [12] wrote that it was probable that the macrophages (and in his macrophage system is found the first suggestion of a reticulo-endothelial system) represented the principal source of antitoxin. Since then it has been shown by Hahn, Von Skramlik and Huenermann [13] that the perfusion of the liver of a sensitized animal absorbs the corresponding antigen. The stellate cells of Kupffer are assumed to be the active agents in the liver. Ehrlich and Morgenroth [14] observed that in dogs poisoned by phosphorus, with a consequent degeneration of the liver, there was a diminished production of alexin or complement. Although later experiments have not by any means settled these questions, there can be no doubt that the reticulo-endothelial system, and consequently the stellate cells of the liver, play an important part in the taking up and destruction of bacteria and in the altered reaction of the body to introduced bacteria.

If next we turn to the circumstances under which bacteria invade the tissues and settle in the liver and consider that, aside from the fact that in very many infections where organisms are introduced through the skin or through the genito-urinary system, the respiratory system, the mouth, the pharynx and œsophagus, and in which bacteria gain entrance into the systemic

circulation and are widely distributed, there is a large group where invasion occurs through the portal system.

Numerous observers have studied the intestinal flora. We all know that multitudes of bacteria, aërobic and anaërobic, inhabit and flourish in the large intestine and the lower portion of the small intestine, becoming less and less under normal conditions as the upper jejunum is reached. The intact epithelial cells, the protective mucus, the continual movement onward of the intestinal contents, all prevent the passage of bacteria through the intestinal wall. Slight alterations, such as congestion or catarrhal inflammation and demonstrable morphological lesions may, of course, alter conditions so that the intestinal wall is penetrated. Fifty years ago Pasteur and his collaborators showed that the anthrax bacillus which is so fatal for mice and guinea pigs, could be swallowed with impunity. To produce anthrax invasion by the path of the intestine it was necessary to feed the animals powdered glass and sand.

I wish, however, to call your attention to a number of experiments which show that bacteria can pass through the normal intestinal wall. There is mention by Metchnikoff [15] of an unpublished paper by Mitchell on experiments carried out in his laboratory, in which animals were killed by the invasion of anthrax bacilli through the intestinal mucosa, to all appearances normal and in which the animals received no nourishment capable of producing lesions of the intestinal wall. The animals were fed anthrax spores mixed with a pap of bread soaked in milk. In 1894, Macallum,[16] in studying the absorption of iron, showed that leucocytes could pass out into the intestinal lumen, take up foreign material and return through the intestinal wall. He recovered the leucocytes containing stained granules in the liver and spleen. The leucocytes found their way into both the systemic and portal circulation. The next year, Desoubry and Porcher [17] working in Nocard's laboratory, established by numerous experiments that during digestion bacteria of all kinds may pass through the normal mucous membrane of the intestines and may be found during several hours in the chyle and blood. These experiments were made at the suggestion of Nocard, who had noticed that serum obtained from blood withdrawn with every possible care from horses shortly after feeding was, every now and again, contaminated.

In studying the pathogenesis of tuberculosis a number of experimenters have confirmed these observations. During digestion many bacteria pass through the intestinal mucosa with the chyle and are found in the mesenteric glands, in the lymph of the thoracic duct, in the blood current and in the liver, spleen and bone-marrow. The younger the animal the more constant the results. The bacteria find their way through the mucous membrane of the intestinal wall without leaving a trace of their passage. Calmette and Van Steenberghe [18] studied the mechanism of passage. They confirm the observations of Macallum. Polymorphonuclear leucocytes in large numbers pass through the mucosa into the lumen of the bowel normally. They form, with the epithelial débris, a not inconsiderable part of the fæces. Attracted by chemotaxis to the surface of the intestine and the secreting surfaces of the

glands, hundreds of thousands pass out daily. Bacteria in the intestinal lumen are taken up by some of these phagocytic cells. During digestion, especially when bacteria are intimately mixed with the food, the bacteria are carried by the leucocytes back through the intestinal wall to enter with the minute globules of fat or the salts of fatty acids, made by breaking up the fats, into the lymph vessels of the villi of the small intestine and hence to the systemic circulation or they find their way to a less extent into the capillaries of the villus and to the portal circulation.

The bacteria taken in may be destroyed by the intracellular ferments of the leucocytes; or the leucocytes containing microbes may be arrested and destroyed in the submucous lymphatics or in the lymph-nodes. However, not infrequently living bacteria reach the liver and are destroyed there. Ford [19] showed that 70 per cent. of the livers removed aseptically a minute or two after death yielded cultures of microbes similar to those found in the intestine. The bacteria seemed to be feeble and attenuated and were slow to grow. The presence of tetanus antitoxin in the serum of individuals who carry tetanus bacilli in the digestive tract has been shown by Ten Broeck and Bauer.[20] They showed spores of tetanus bacilli in 34 per cent. of the stools of 78 individuals in Peking. May it not be assumed that here we have an instance of a reaction being set up by spores absorbed during digestion and carried to the liver? Obviously, the nature of the bacillus, the character of the food, the species of animal, may all cause wide variation. The fatty and waxy coating of the tubercle bacillus, for example, makes it particularly resistant to the intracellular ferments of the leucocytes.

The question as to the reaction set up in the liver by the lodged bacteria is equally interesting. That bacteria, without the signs of tissue reaction, can be found in both the liver and the gall-bladder, has been pointed out by Aschoff.[21] He had a large number of unchosen livers examined for possible inflammatory reactions. He concludes that although staphylococci, streptococci and pneumococci can be more or less frequently demonstrated bacteriologically, yet the gall-bladder and the intrahepatic bile passages may be normal in appearance and therefore that certain bacteria may be excreted through the liver and perhaps through the gall-bladder without a special reaction.

Adami [22] pointed out that, in conditions of congestion and slight chronic inflammation, bacteria may, time after time, pass through the intestinal wall to be deposited and destroyed in the liver. The microbes may not necessarily multiply in the organ. Repeated inroads and repeated destruction of bacteria, however, yield enough toxic substances to produce an appreciable alteration in the parenchymatous cells. He suggested the term subinfection to describe the reaction.

The reaction in the reticulo-endothelial cells, when considerable numbers of microbes are introduced into the blood, has been made the subject of an interesting study by Oerskov.[23] He used more or less virulent strains of streptococcus, staphylococcus, pneumococcus and bacillus coli. He destroyed

the animals at varying intervals from five minutes to several days after the injection. He studied the amount of phagocytosis by the Kupffer cells and the amount of exudation of leucocytes. He found in animals killed after two minutes many cocci in the liver and a few in the spleen. The cocci were largely inside the Kupffer cells. The leucocytes were few. In an hour and a half all the Kupffer cells were packed with cocci and there was a considerable exudation of leucocytes. At the end of six hours the liver contained a great number of cocci and the leucocytes were in great numbers. At the end of eighteen hours there were still a large number of microbes in the liver but many of them stained poorly; the leucocytes were numerous. At the end of eight days the microbes were no longer found. In the destruction of the cocci by the Kupffer cells there was pronounced infiltration of the interstitial tissue with leucocytes; similar results were obtained in studying the destruction of other microbes. None of the polymorphonuclear leucocytes showed evidence of phagocytic activity.

In another series he introduced a fatal dose of pneumococci. The results were similar up to a certain time. The cocci were rapidly arrested and destroyed in the liver by the Kupffer cells, accompanied by the same infiltration of the interstitial tissue by leucocytes, but at the end of twenty-four hours there was a multiplication of the pneumococci. The protective cells were unable to hold in check the microparasites and the body was invaded.

According to the type of organism and the degree of immunity established in the body, not only an exudative inflammation occurs, but various forms of degeneration, necrosis and regeneration, and various forms of productive inflammation, giving the most varied picture of interstitial and parenchymatous lesions.

Chronic productive inflammation of the interstitial tissue is very frequent and leads to a variety of alterations in the liver tissue which are grouped under the general heading cirrhosis.

There is a wide margin of safety in the liver. Rous and MacMaster [24] have shown in the dog and the monkey that three-fourths of the secreting cells of the liver can be shut off without producing symptoms. That considerable cirrhosis can exist without clinical symptoms has long been well recognized.[25]

There can be no question that the liver is concerned in the defense mechanism of the body. It is concerned normally in the disposal of and making innocuous various substances brought to it; in the exaggeration of this function various reactions occur which are shown morphologically. The liver seems to be one of the first organs to react and forms a first line of defense, as it were in the protection of the body against disseminated bacteria.

Many of these reactions pass without evidence of disturbance, such as fever, etc., which can be recognized clinically. There is an interesting hypothesis of Vaughan [26] in this connection. He suggests that when bacteria are destroyed, the general body reaction, the heightened metabolism, the rise of body temperature, all the general disturbances that we group under fever,

are due to the disintegration of foreign bacterial proteins by extracellular ferments. The destruction of bacteria inside the cells may be unaccompanied by these phenomena. The intracellular ferments in the macrophages (Von Kupffer cells) carry perhaps the destruction of the bacterial proteins to a point where the products are much less toxic or build them up into their own protein. The process of intracellular digestion may pass so smoothly that the host may be unaware of the bacterial destruction going on and present no disturbance of the normal working of the body that can be recognized clinically.

The large phagocytic cells of the reticulo-endothelial system have another function. They are concerned in the destruction and disposal of red blood-cells. This has been shown to take place normally in the liver, the spleen, the bone-marrow and the lymphatic nodes. The hæmoglobin is split into an iron-containing portion and an iron-free portion and the liver seems to play an important part in the disposal of both portions. When the red cells are destroyed in excess the iron accumulates in the liver. The iron produced in excess in the reticulo-endothelial system is released into the circulation and stored and slowly secreted by the liver cells. It shares this function of storage with the spleen and takes it over when the spleen is removed.

The disposal of the iron-free portion has been the subject of much study. It is concerned in the production of bilirubin. There has been much controversy over the site of the formation of bile pigment and the production of jaundice. In the well-known experiments of Naunyn and Minkowski [27] the liver was removed from a goose; then the bird was poisoned with arseniureted hydrogen. No icterus followed. In another experiment the liver was not removed. In this instance poisoning by arseniureted hydrogen resulted in an enormous phagocytosis of erythrocytes and the production of jaundice. The text-books of physiology of fifteen years ago record the famous experiments. But as almost all the reticulo-endothelial cells in birds are in the liver, the spleen and bone-marrow containing relatively few cells of this system, these experiments were inconclusive when applied to mammalia.

Later, Whipple and Hooper [28, 29] excluded the portal circulation in dogs, injected hæmoglobin and were then able to show bile pigment in the urine, and Mann and Magath [30] observed the formation of bilirubin in dogs after the removal of the liver. The text-books of physiology of the future will record these experiments. It seems to be established to-day that one of the functions of the reticulo-endothelial system is the production of bilirubin. The Kupffer cells of the liver make up an important part of this system, so that although there is an extrahepatic formation of bilirubin, it by no means implies that the liver is not the seat of a considerable portion of bile pigment production. Of the polyhedral cells of the liver it may perhaps be said that the evidence to-day is against their ever sharing in the formation of bilirubin. They excrete the pigment but do not form it. The bilirubin made by the reticulo-endothelial cells seems to be slightly different from the bilirubin secreted by the liver. Van den Bergh [31] showed that these differences could

be detected by the behavior of the pigment in the diazo reaction. These differences are possibly due to physical changes in the state of the bilirubin in the plasma. The bilirubin acted on by the liver cells diffuses more readily and is more readily oxidized. It gives what is known as the immediate or direct reaction. The bilirubin, as it is formed by the cells of the reticulo-endothelial system, diffuses less readily and is less readily oxidized. It gives a delayed or indirect reaction.

Concerning the secretion of bile salts and cholesterin, little definite is known. It is assumed by Brulé [32] and a number of French observers that the polyhedral cells have a selective action, very much as the secreting cells of the kidney have. At times, when the cells are damaged, now one, now another ingredient is not excreted by the polyhedral cells so that there may be the presence of bile salts alone or bilirubin alone in the blood. There is not always a complete retention of all the component parts of the bile. Unfortunately the tests for the detection of the bile salts in the urine are open to criticism. However, his work is interesting and suggestive. The itching, the brachycardia, the absorption of fat, are all said to be due to bile salts. He thinks obstructive jaundice is "globale et brutale"; both salts are retained completely and suddenly. In hepatitis from various toxic substances the dissociation of the two substances found in the bile exists, now one, now the other appearing in the serum, then both appear, and again in the disappearance of the jaundice there is a similar irregularity.

The liver is, as we have said, concerned in the storage and detoxication of various substances besides bacteria. When colloidal metals are injected into the circulation they are taken up by the Kupffer cells. If the dosage is sufficient the cells are injured. The damaged function is made evident by the clinical sign of jaundice and the extent and character of the jaundice is, in a way, a measure of the impairment of the liver cells. Cunningham,[33] in studying the clinical effects of colloidal lead in patients to whom it had been administered for inoperable carcinomata, describes three forms of jaundice:

I. There is a slight icteric change in the sclera with increased urobilin and a positive indirect or delayed direct Van den Bergh reaction. The bile secreting cells are probably unaffected. The jaundice is due to excessive production of hæmolysis by the Von Kupffer cells and the reticulo-endothelial system. The pigment is produced in too large quantities to be taken up directly and secreted by the polyhedral cells of the liver parenchyma, with the result that a quantity continues to circulate in the blood.

II. There is damage to the polyhedral cells of the liver, urobilin and bile appear in the urine, the jaundice is deeper, the Van den Bergh reaction is biphasic or of direct type.

III. In the third type there is evidently a cholangitis in addition, due to the destruction of the polygonal cells. Jaundice is deeper and there are large amounts of bile in the urine. There may or may not be an increase of bilirubin of the urine; the van den Bergh test is immediate or direct.

These studies seem to me of especial interest. They furnish an indication of the way certain toxic substances act in producing jaundice by direct action on the reticulo-endothelial cells and on the polyhedral cells of the liver. We have in jaundice an obvious clinical sign and, in certain cases, an indica-

tion of the disturbance of function, either in the secreting polygonal cells of the liver or in the Kupffer cells. A similar relation of jaundice to the irritation of microbes deposited in the liver exists.

In 1916, Inada and Ido [34] and their co-workers showed the presence of spirochætæ in the blood, liver and kidneys of patients suffering from an epidemic and an endemic form of infectious jaundice occurring in Japan. They transmitted the spirochætæ by intraperitoneal injections in guinea pigs and cultivated the microparasites outside the body.

The action of the spirochætæ in producing the jaundice cannot be easily explained by obstruction of the bile passages. In the severe cases the bile passages are pervious. The lesions are confined to the hepatic cells. During the first days of the disease, before the appearance of the jaundice, the spirochætæ can be demonstrated in the blood. But the spirochætæ do not remain long in the general circulation. From the fifth to the eighth day inoculations of guinea pigs with the blood are negative; enough immunity is established to destroy the parasites in the circulating blood. The microparasites are found in the liver and other organs. Moreover, all grades of jaundice are produced. In certain cases there is no jaundice, in others it is slight and transitory, like a mild grade of catarrhal jaundice; in others it is severe and gives the picture of acute yellow atrophy. In reading the accounts of the disease it is difficult not to see a resemblance to the occasional cases of so-called acute catarrhal jaundice and there has been a general tendency during the last ten years to place fewer and fewer cases under the heading of catarrhal jaundice. The majority are assumed to be sporadic cases of infective hepatitis. Not that there is any general assumption of a spirochætal origin for all forms of epidemic jaundice. In an article by Blumer [35] in 1923, he expressly states that in the types of the disease which he has had an opportunity to see, no spirochætæ were demonstrated and that he believed that they were not the causative agents in the types usually seen in this country. But the relation of epidemic forms of jaundice to catarrhal jaundice is too striking not to assume that the ordinary forms of catarrhal jaundice are but sporadic cases of infectious jaundice, and the resemblance of the epidemic infectious jaundice is too similar to the disease produced by spirochætæ not to be noted. The clinical picture of the fatal cases, which are rare, is that of acute yellow atrophy, just as in spirochætal jaundice and here again all the evidence seems to point to hepatitis as the cause of jaundice. It is understood, of course, that acute yellow atrophy is not a disease entity but a syndrome produced by a number of toxic agents.

The autopsies which showed any lesions which corresponded to older theories of catarrhal jaundice are very few. The case reported by Eppinger [36] is of interest. A girl nineteen years old, suffering from acute catarrhal jaundice, in a fit of despondency threw herself out of a window. At autopsy the inferior extremity of the common duct was found blocked by a mass of inflamed lymphoid tissue.

The evidence to-day makes it probable that a large group of transitory

jaundices are due to damage to the liver cells, not to obstruction from catarrhal inflammation. Many microbes set up an infective hepatitis and certain of them have an elective affinity for the liver, localize there and create lesions more or less grave.

In most of the acute infections there is a period when the microparasites are found in the blood stream. Here again, after a period during which a certain degree of immunity has been established, they disappear and are found deposited in the liver and other organs. In typhoid, in pneumonia, in secondary syphilis, in malaria, etc., jaundice is occasionally present. In streptococcal sepsis and other forms of sepsis, jaundice occasionally occurs. In the fatal cases at autopsy, aside from various parenchymatous and degenerative changes, the liver shows frequently a round-celled infiltration in the interstitial tissue and focal necrosis.

Here, again, it is difficult not to believe that some degree of hepatitis is almost always present and that, now and again, either due to some special weakness, predisposition or sensitization, the parenchyma cells are enough involved to interfere with their normal function of excreting bile. The obvious clinical sign of jaundice occurring every now and again in the course of disseminated bacterial invasion, is an indication of the hepatitis which is, in all probability, frequently present and is comparable to the jaundice seen occasionally during the administration of certain toxic substances.

It is interesting to see how often transitory infective icterus appears in subjects in which the liver is already the seat of a lesion, from alcohol, syphilis or pregnancy. Possibly toxic substances set free in the violent reaction of the Kupffer cells to the multiplying microbes produce changes in the polygonal cells, disturb their function and hinder secretion. The margin of safety is so great in the liver that such hepatitis must be widespread to produce jaundice. The study of the pathogenesis of spirochætosis has transformed the significance of jaundice. It has placed a large group formerly classed as obstructive jaundice under the jaundices due to action of microorganisms on the liver cells and has called attention to the reaction of the liver cells regularly present in disseminated infection. Even in obstructive jaundice, where the main excretory ducts are closed, the liver cells are rapidly implicated. If there is obstruction of the hepatic duct above the point where the gall-bladder enters or if the common duct is completely shut off, after the gall-bladder has been removed, there may be such a disturbance of the liver cells that no bilirubin is secreted. The ducts contain whitish matter made up only of the excretions of their walls, but the failure of the liver cells to secrete bilirubin is not due to failure of the pigment to be formed. The evidence all goes to show that the bile suppression is due to a disturbance of the liver cells, and only indirectly to an obstruction to the outflow. If the gall-bladder is in place then the back pressure on the secreting cells is not so great and the damage is much less.[37] If the obstruction is intermittent, infection, either ascending or descending, inevitably follows and widespread cholangitis with further involvement of the liver cells occurs.

Various microbes not only settle out and are taken up by the liver cells in the course of disseminated infection, but reach the interstitial tissue of the liver in clumps or masses from a disintegrating, infected clot in the portal vein or by emboli through the hepatic artery, being arrested in the small vessels and producing a variety of focal lesions and multiple or single abscesses.

It has long been recognized that patients suffering from amœbic dysentery not infrequently develop liver abscesses. The amœbæ spread in the submucosa of the intestines. They may be found both in the blood-vessels and lymphatics, to be carried to the mesenteric lymph-glands or through the portal circulation to the liver, where they set up a hepatitis. The hepatitis may subside or, if the tissue resistance is poor or the dosage massive, abscesses form. Here again the liver is the first great barrier to the dissemination of the infecting agent.[38]

In many of the stages of infection when a partial immunity has been established, various forms of hepatitis occur, often giving little or no clinical evidence of their presence. According to Calmette,[39] during the course of infection with tubercle bacilli, small tuberculous lesions are nearly always present in the liver if careful enough search is made. In an autopsy reported by Sabrazes,[40] in a patient who died of leprosy, the liver showed no leprous nodules, but sections showed an enormous phagocytic reaction of the Kupffer cells. There were no bacilli, however, in the biliary passages; none in the bile. In late stages of syphilis the liver more frequently harbors treponemata than any other organ. Various forms of interstitial hepatitis, as well as the characteristic gummata, are present. Syphilis is relatively frequent. In over nine thousand Wassermann tests, taken as a routine measure in all patients treated at St. Luke's Hospital during the last year, including the out-patient department, over five per cent. showed a positive reaction. As in a number of these repeated examinations were made and as there must be a large number with syphilitic infection, yet showing a negative examination, the actual percentage should be put much higher. It would be interesting if we knew in how many of these patients there were changes in the liver, due to the lodged treponemata.

Anyone connected with a large hospital has an opportunity of seeing all these forms of hepatitis. He gets an impression of an extraordinarily complex etiology.

With these facts in mind, I shall next attempt to study the path of infection suggested in a number of recent papers and the relation of hepatitis to cholecystitis and then of cholecystitis to hepatitis.

In the first place there is a widespread notion that appendicitis, hepatitis and cholecystitis are related and that infection passes from the appendix to the liver through the portal vein. That this relation occasionally exists, in acute cases in which there is a suppurative lesion of the veins in the mesentery of the appendix and a progressive suppurative pyelophlebitis is set up, which leads to infected clots lodging in the liver, is generally recognized. But during the course of acute appendicitis, cholecystitis and hepatitis are not usually

recognized. The associated acute lesions occur, but they are not common. I do not find, in patients operated on for acute suppurative appendicitis, any disproportionate number later developing clinically recognizable forms of hepatitis. Nor do the autopsy records on patients dying of acute appendicitis as a rule show lesions of the liver. Tens of thousands of microörganisms are undoubtedly lodged in the liver, just as they are in the spleen and the bone-marrow in general sepsis from acute appendicitis. They are taken out of circulation and many of them are destroyed in these situations. Nor is the proof offered that hepatitis has been found, in removing sections of liver while performing appendectomy for chronic appendicitis, convincing. The sources of error are obviously too numerous; the impossibility of excluding other inciting agents is too great; the number of observations are too few.

Nor do I find evidence that cholecystitis regularly follows hepatitis. In the numerous instances of infective hepatitis I can find only occasional instances of involvement of the gall-bladder which reaches the grade of clinical recognition. Although hundreds of thousands of microbes are lodged in the liver there is only very exceptional evidence of acute cholecystitis. I do not question that if these patients were operated on, various slight degrees of round-celled infiltration of the wall of the gall-bladder might be found, but during the course of the jaundice that is so frequently present in infective hepatitis there is rarely present a form of cholecystitis that can be recognized clinically.

During the last year I have twice operated through a mistake in diagnosis on patients with infective hepatitis. A woman aged thirty-seven years, entered the hospital acutely ill with a temperature and jaundice. She was kept under observation. There was a history of syphilitic infection and treatment by salvarsan five months previously and, although she had had little pain, having only a sense of fulness and distention after meals, and gave no history of having had attacks suggesting cholecystitis, the erroneous conclusion was reached that she had an obstructive jaundice. On opening the abdomen the gall-bladder was full but could readily be emptied. There were no adhesions, the wall was thin, there was no dilatation of the ducts, the liver seemed a little firm. A section removed for examination showed the lesion of severe, extensive hepatitis, the lesion extending about the minute bile ducts and about the portal venules. The gall-bladder was anastomosed to the stomach. The patient made a good recovery; the jaundice very slowly subsided, as is the rule in infective jaundice. The patient, seen one year and a half later, was in good health, with no jaundice. There was marked hepatitis, proved by the microscopical section, and no appreciable cholecystitis. The second case was similar. There was hepatitis present; the gall-bladder and ducts seemed normal. The patient had an infective hepatitis imposed upon a cirrhosis of the liver.

The following case report is in point: A man aged forty-one years, entered the hospital very ill, with fever and general abdominal pain. He was slightly jaundiced. The abdomen was opened through a right rectus incision; the gall-bladder seemed normal, a

gangrenous retrocæcal appendix was discovered and removed. He grew gradually more jaundiced and died on the second day. During the last day he complained bitterly of pain in his right leg. At autopsy the liver showed marked hepatitis. The common duct was patent and there was no dilatation. The cystic duct was patent; there was no gross lesion of the gall-bladder. There was infection of the retroperitoneal tissue; the psoas muscle was soft and pultaceous. Cultures from the retroperitoneal infection showed a large non-gas-forming bacillus. This patient is an example of hepatitis following appendicitis, yet advanced acute hepatitis was unaccompanied by gross lesions of the gall-bladder.

In typhoid fever the relation of hepatitis and cholecystis has attracted much attention. The initial period of typhoid fever is accompanied by the presence of typhoid bacilli in the blood stream. After a time the bacilli are no longer found in the blood. They are found in the bone-marrow, spleen, lymphoid tissue of the intestine and lymph-glands of the mesentery. In the lymphoid tissue of the intestine they colonize, multiply and produce the characteristic lesions of the disease. The livers of patients dying of typhoid regularly show changes; there is fatty degeneration, infiltration with leucocytes, masses of leucocytes about degenerated and fragmented liver cells. These nodules are said to be due to bacterial emboli.[41] At times there is acute diffuse hepatitis or massive fatty degeneration, some of these patients are jaundiced and the jaundice, to quote Widal, is due to a hepatitis: "The jaundice of typhoid is really a hepatitis, the result of lesions of the hepatic cells, determined by the localization in the liver of microbes deposited there from the general circulation.[42] The bile regularly contains typhoid bacilli and there are all grades of lesions of the gall-bladder, from catarrhal to purulent inflammation, yet cholecystitis giving clinical symptoms is not common in typhoid fever. From the seventh to the thirtieth day pain in the right hypochondrium, tenderness and rigidity are the symptoms that all who have an opportunity to see any considerable number of patients suffering with typhoid, associate with the condition. Though thousands of microorganisms are in the blood stream and the liver and although the gall-bladder wall frequently shows lesions, only occasionally do symptoms appear that bring the lesions into the plane of clinical observation. Other factors seem to be necessary. One would expect that occasionally bacterial emboli might be lodged in the wall of the gall-bladder. One would expect that occasionally bacteria would be carried by the lymph stream to the wall, but it is difficult not to believe that the thousands of organisms in the infected bile must play a most important part in producing lesions of the gall-bladder. The experiments of Nichols are suggestive.[43] He succeeded in 63 per cent. in producing gall-bladder lesions when injecting typhoid bacilli by the mesenteric vein and in 41 per cent. when injecting into the systemic veins. There was a considerably higher percentage of gall-bladder infections occurring in the immune animals than in the normal animals. He brought forward the view that gall-bladder infections in inoculated animals are not necessarily an index of immunity, but may be in part an indication of a rich amount of immune bodies in the blood.

The colon bacillus, aside from infection of the liver following stones lodged in the common duct and consequent infective cholangitis, can, in exactly similar manner, cause jaundice. The following autopsy report is an example: The skin was jaundiced, the liver showed acute hepatitis, the common duct was normal in appearance, the gall-bladder showed a subacute lesion. There was extensive degeneration of the liver cells and central necrosis, yet the gall-bladder showed only a subacute lesion. Cultures taken from the gall-bladder bile showed colon bacilli.

In the purulent form of interstitial hepatitis it is curious to see the absence of correspondence in the lesions of a gall-bladder and the lesions of the liver. A child, ten years old, very ill, was admitted to the hospital. She had a high temperature, tenderness and an indistinct feeling of mass in the right hypochondrium. The abdomen was opened, the liver was found enlarged, the gall-bladder seemed acutely inflamed. It was removed. The patient died in three days. At autopsy there was only a small amount of serous fluid in the upper part of the abdomen. There were no signs of peritonitis. The liver was enlarged and riddled with abscesses. There was an early parietal clot forming in the portal veins. Section of the gall-bladder removed at operation showed a subacute cholecystitis. Although the liver was filled with abscesses, some of them but a few centimetres from the gall-bladder, only enough bacteria had passed through the lymphatics to set up a subacute lesion. Cultures from the pus in the abscesses showed colon bacilli.

In amœbic abscesses I have been unable to find records of gall-bladder involvement. Although tubercular lesions of the liver are said to be common, tuberculosis of the gall-bladder wall is rare. Simmonds [44] has given a description of the forms. In syphilis, although various forms of hepatitis are common, there is no evidence of unusual frequency of clinical forms of cholecystitis. As I understand the evidence, there is no unusual incident of gall-bladder infection following the various forms of hepatitis. Bacteria are probably not infrequently present and not infrequently there are slight evidences of an inflammatory reaction. To produce a clinical form of cholecystitis, added factors are necessary.

If the gall-bladder is grossly infected, if the bacteria are lodged in its wall and the tissues react and the lumen is filled with exudate and bile, does a form of hepatitis develop, leading to clinical forms of cirrhosis? A reacting zone of contiguous structures is formed about the inflamed organ. The peritoneum, the wall of the colon and the duodenum are glued to the gall-bladder by exudate. The omentum turns up and is adherent to the gall-bladder and the edge of the liver; the cellular tissue between the gall-bladder and the liver reacts and the interstitial tissue of the liver reacts. The extent of the zone of circumscribing reaction depends, as in all infections, on the virulence of the lodged organisms and the local and general resistance. There are all grades of severity, from inflammatory changes that can hardly be detected by microscopical study, to changes where purulent exudate and ulceration and necrotic processes are the characteristic features; and in all

of them the liver in contact with the gall-bladder shows varying grades of hepatitis. Moreover, if the attacks are repeated there may be evidences of chronic interstitial inflammation. Sections taken of the quadrate lobe or the right lobe in the neighborhood of the infected gall-bladder regularly show signs of inflammation on microscopical examination.

Anyone who has operated on a number of gall-bladders recognizes, as a matter of course, the infiltration of the cellular tissue between the gall-bladder and the liver, succulent in fresh infection, dense and firm in long-standing cases. When the gall-bladder ulcerates or is necrotic at some point an abscess may form partially in the liver substance. There can be no question that some form of local hepatitis occurs in almost all infections of the gall-bladder and that the infection travels from the gall-bladder to the liver. It is a matter so generally accepted that it has rarely been emphasized. It is part of the pericholecystitis nearly always present. Specimens, however, have been taken in many instances far enough away from the bed of the gall-bladder to indicate that the reaction is widespread. There is no means of knowing in these instances whether the reaction in the liver may not be due to one of the many irritants which reach the liver. This may readily be the case if the gall-bladder lesion does not present gross morphological changes. In any event, the hepatitis which we see so frequently at operations for cholecystitis does not seem to have clinical significance, for if the grossly inflamed gall-bladder is removed there is no progressive involvement of the liver. In several cases in which I have removed a gall-bladder with an abscess between the gall-bladder and the liver, the infection in the liver has apparently promptly subsided, for these patients are in good health and fat when seen years after their operations.

A patient entered the hospital two years ago presenting several interesting features. He had a bottle in his hand containing gall-stones that he had passed twenty years ago. He had had, after this long period of latency, a severe attack of typical gall-bladder pain. Twenty-seven years ago he had had his first attack and during seven years following had had a number, several of them with jaundice. During the last one of these attacks he passed the stones he showed. He was operated on by Doctor Bolling and an obviously inflamed gall-bladder was removed, containing stones in every way similar to the ones he had passed many years before. The liver seemed firm and the edge a little rounded. The wall of the gall-bladder showed a small carcinoma. He had at that time and still has, two years later, no signs of chronic hepatitis or liver cirrhosis that can be appreciated clinically, although there had been enough irritation to produce a new growth, and although the irritating agent had acted over a period of twenty-seven years.

There is another bit of evidence worth recording. Fifteen years ago, in a number of the large clinics, the gall-bladders were not removed. The stones were removed and the gall-bladder drained. The practice was abandoned. There were too many recurrences due to impacted stones or stenosis of the cystic duct. Many of these patients recovered. I can recall no instance

or report of the retained, grossly infected gall-bladder setting up chronic forms of hepatitis. I gained the impression at that time that a draining gall-bladder, even if infected, gave little or no symptoms.

In deeply jaundiced patients with septic fever and a stone in the common duct, I have in several instances left the shrunken gall-bladder in place, opened the common duct and removed the stones. In no instance has a progressive hepatitis or liver cirrhosis followed.

I do not find evidence, then, of a so-called vicious circle; a chronic appendicitis, then a hepatitis, then a cholecystitis and the cholecystitis then becoming the main focus and producing hepatitis. The evidence seems to be that the liver is a most efficient filter for bacteria, taking them up from the general or portal circulation and that only a few pass the cells of the peculiar liver capillaries to reach the lymph and float along with the lymph current into the nodes at the hilus. At autopsy or at operation these nodes are not infrequently enlarged, but the enlargement of the lymphatic nodes is an inconspicuous feature of infective hepatitis. I do not question that a few bacteria may pass along the lymphatics from the liver into the wall of the gall-bladder. I do question, however, whether slight infiltration of the gall-bladder wall, changes so slight that it is impossible to recognize them by gross examination, are clinical forms of cholecystitis. This assumption seems to be based on the observation that certain patients gain relief from symptoms of a form of dyspepsia after the removal of a gall-bladder which shows no macroscopic lesions or shows beneath the mucosa, when cut open, small yellow spots from lipoid deposits (strawberry gall-bladder). This form of indigestion is shown by accumulations of gas in the upper abdomen, belching, sour regurgitations occurring promptly after eating a hearty meal or badly prepared or indigestible food.[49] Unfortunately these symptoms are present to some degree in most middle-aged people. They are present, as I have assured myself, at times after the gall-bladder has been removed and they are absent in many instances in which there is a gross lesion of the gall-bladder wall.

In the same way study of the cholecystograms, made by the method recently introduced by Graham, has been said to furnish a surer means of recognizing gall-bladder disease than the sight and touch of the surgeon at operation; that is, by the observation of the filling and emptying of the gall-bladder one can determine whether a gall-bladder is so diseased that it should be removed, even if there is no demonstrable lesion at operation. The gall-bladder disease is proved by the microscopic examination of the excised gall-bladder wall, showing a very slight cellular infiltration and by statements made by the patients of relief after operation. But is it not too early to draw this conclusion; is not too little known of the normal function to speak so confidently of abnormal functions? I grant that certain patients get complete relief after operations for the removal of the gall-bladder with very trifling lesions of the gall-bladder wall, but a more or less lasting freedom from symptoms has been presented as proof for all manner of remedies. Patients treated by homeopathy and osteopathy are sincere in their belief

in the remedies applied and grateful for the relief afforded. I believe we should demand stronger proof. I have an instinctive distrust of occult surgery or surgery for occult lesions. I recently saw a middle-aged woman operated on in a large clinic. Her symptoms were, as nearly as I can remember, gas, indefinite gastric discomfort, inability to eat certain foods, and pain after eating. When the gall-bladder was exposed it was soft, thin-walled, on manipulation it emptied, there were no adhesions, no stones. The gall-bladder takes up and concentrates bile and regulates the pressure in the biliary system.[47] If the orifice of the cystic duct is blocked, there is evidence of disturbance and pain. The gall-bladder in question emptied, it was thin-walled and distensible. It contained stasis bile. Which of its known functions was at fault? The gall-bladder was removed, it was cut open and from the appearance of the thick, stringy stasis bile, cholecystitis was said to be present.

The pathologist, Aschoff,[48] whose painstaking and thorough studies have thrown so much light on the formation of gall-stone and the function and structure of the extrahepatic bile passages, has pointed out that in studying post-mortem staining of the biliary passages there are fairly constant findings. The region of the sphincter of Oddi is usually pale, almost colorless, a sign that it is closed, even after death. The common and hepatic ducts and the cystic duct up to the neck of the gall-bladder are stained yellow, that is, stained with hepatic bile, while the neck and the rest of the gall-bladder are stained dark brown by the stasis bile of the gall-bladder as if the change in color marked a division between the conducting system and the condensing system of the extrahepatic bile passages. He also points out that there is sphincter-like thickening of the smooth muscles at the beginning of the cystic duct and numerous ganglion cells and nerve fibres in the wall of the cystic duct. We apparently have to think not only of the mechanism of control at the orifice of the common duct, but of a mechanism of control at the outlet of the gall-bladder. That among the patients in whom the gall-bladder has been removed for trifling lesions and in whom the cysticus is patent, there are a few who have had definite cramp-like attacks due to disturbance of the nervous control mechanism which synchronizes the various sphincter-like structures at the orifice of the cystic and at the orifice of the common duct, seems very probable. But in the great majority of cases, to produce a clinical form of cholecystitis, either very unusual virulence of the microörganisms is necessary or there is added to the factor of slight infection a disturbance either mechanical (calculus, anatomical peculiarities, etc.), or functional, which interferes with the passage of the gall-bladder contents through the cystic duct.

TO SUMMARIZE

I. One of the main functions of the liver is the destruction and disposal of bacteria and toxic substances.

II. Bacteria and toxic material reach the liver in a great number of ways and very frequently throughout life.

III. Some are destroyed there without appreciable reaction and all grades of appreciable reaction occur.

IV. The morphological changes which occur in the liver in the reaction of the cells to irritants and which are called by the pathologist hepatitis are extremely difficult to classify. The subject of hepatitis is one of the most complex in the domain of pathology. It is in no sense an entity nor can it be discussed with profit as an entity.

V. Many of the cases formerly grouped under acute catarrhal jaundice are now considered forms of infectious hepatitis.

VI. In the forms of hepatitis which have reached the level of clinical observation there is little evidence of a relation to clinical forms of cholecystitis.

VII. The hepatitis regularly found with cholecystitis has little or no clinical significance and is not a factor of importance in causing clinical forms of liver cirrhosis.

VIII. The proof that very slight infiltration of the gall-bladder wall and lipoid deposit in the mucosa cause acid indigestion, a feeling of fulness in the epigastrium, flatulence, intermittent gastric pain after eating badly prepared food, is by no means conclusive.

In closing, may I quote the following letter of advice to a young noblewoman from Burton's *Anatomy of Melancholy:* " In this hypochondriacal or flatuous melancholy the symptoms are so ambiguous that the most exquisite physicians cannot determine of the part affected." The symptoms of this disease are said to be " sharp belchings, fulsome crudities, heat in the bowels, wind and rumbling in the guts, vehement gripings, pain in the belly and stomach sometimes, after meat that is hard of concoction." I am not sure whether Burton's rendering is better than the original Latin, which I add: " Acidi ructus, cruditates, æstus in præcordiis, flatus, interdum ventriculi dolores vehementes, sumptoque cibo concoctu difficili."

BIBLIOGRAPHY

[1] Graham: Hepatitis a Constant Accompaniment of Cholecystitis. Surg., Gyn. and Obs., 1918, vol. xxvi, p. 521.

[2] Graham: Further Observations on the Lymphatic Origin of Cholecystitis. Arch. of Surg., 1922, vol. iv, p. 22.

[3] Graham: New Developments in Our Knowledge of the Gall-bladder. Am. Jour. Med. Sc., 1926, vol. clxxii, p. 625.

[4] Aschoff: Concept of Inflammation. Lectures on Pathology, 1924, p. 74.

[5] Krogh: The Anatomy and Physiology of Capillaries, 1922, p. 64.

[6] Schafer: Essentials of Histology, 1920, p. 364.

[7] Sappey: Les Lymphatiques, Traité d'Anatomie, Poirier, 1909, p. 1226.

[8] Roger: Physiologie Normal et Pathol. du Foie, 1922.

[9] Graham: Resistance of Pups to Late Chloroform Poisoning in Relation to Glycogen. Jour. Exp. Med., 1915, vol. xxi, p. 125.

[10] Wyssokowitsch: Ueber schikasle der in's blut injioirten mikroorganismen, im korper der warmbluter. Zeitsch. f. Hyg., 1886, vol. i, p. 3.

[11] Nichols: Experimental Observations on the Pathogenesis of Gall-bladder Infection in Typhoid, Cholera and Dysentery. Jour. Exp. Med., 1916, vol. xxiv, p. 497.
[12] Metchnikoff: L'Immunité, 1901, p. 421.
[13] Hahn, Von Skramlik and Huenermann: Aschoff, Reticuloendothelial System. Ergebnd. inn. med. und kinder., 1924, vol. xxvi. (Bibliography.)
[14] Ehrlich and Morgenroth: Zinsser's Infection and Resistance, 1923, p. 189.
[15] Metchnikoff: *L. c.*, p. 444.
[16] Macallum: Jour. of Physiol., 1894, vol. xvi, p. 288.
[17] Desoubry et Porcher: De la presence de microbes dans le chyle normal chez le chien. Soc. de Biol., 1895, p. 101.
[18] Calmette and Van Steenberghe: Annals of Pasteur., 1910, p. 316.
[19] Ford: Jour. of Hyg., 1901, vol. i, p. 276.
[20] Ten Broeck and Bauer: Studies in the Relation of Tetanus Bacilli in the Digestive Tract to Tetanus Antibodies in the Blood. Jour. Exp. Med., vol. xxxvii, p. 47.
[21] Aschoff: Extrahepatic Bile Passages, Lectures on Pathology, 1924, p. 205.
[22] Adami: Subinfection. Jour. A. M. A., 1899, vol. xxxiii, pp. 1506–1572.
[23] Oerskov: Observations sur la propriété phagocytaire. Comptes Rendus, Soc. de Biol., 1925, p. 959.
[24] McMaster and Rous: Biliary Obstruction Required to Produce Jaundice. Jour. Exp. Med., 1921, vol. xxxiii, p. 731.
[25] Delafield: Lectures on the Practice of Medicine, p. 784.
[26] Vaughan: Poisonous Proteins, 1917, p. 86.
[27] Naunyn and Minkowski: Luciani, Physiologie Dell'uomo, vol. ii, p. 165.
[28] Whipple and Hooper: Jour. Exp. Med., 1913, vol. xvii, pp. 593–612.
[29] Whipple and Hooper: Jour. Exp. Med., 1916, vol. xxiii, p. 137.
[30] Mann and Magath: Effect of Total Removal of the Liver. Transactions of Section on Path. and Physiol. Jour. A. M. A., 1921, p. 29.
[31] Van den Bergh: La Presse Médicale, 1921, p. 45.
[32] Brulé: Recherches sur les ictères, 1922, p. 240.
[33] Cunningham: The Clinical Effect of Lead in the Treatment of Carcinoma. Brit. Jour. of Med., Nov. 30, 1926, p. 931.
[34] Inada and Ido: Etiology and Mode of Infection of Weil's Disease. Jour. Exp. Med., 1916, vol. xxiii, p. 377.
[35] Blumer: Infectious Jaundice in the United States. Jour. A. M. A., 1925, vol. lxxxi, p. 353.
[36] Eppinger: Path. der icterus catarrhal. Wein. Klin. Wochen., 1908, vol. xxi, p. 480.
[37] Drury and Rous: Suppression of Bile as a Result of Impairment of Liver Function. Jour. Exp. Med., 1925, vol. xli, p. 611.
[38] Phillips: Amœbiasis, p. 32.
[39] Calmette: *L. c.*, p. 193.
[40] Sabrazes: Leprose Massive de la Rate et du Foie, Comptes Rendus, Soc. de Biol., 1925, vol. xciii, p. 1526.
[41] Widal, Lemierre et Abrami: Maladies Infectieuses, 1924, p. 73.
[42] Widal, Lemierre et Abrami: *L. c.*, p. 123.
[43] Nichols: *L. c.*
[44] Simmonds: Verhandl. d. deutsche path. gesellsch., 1910, vol. xiv, p. 332.
[45] Hartman: Diseases of the Biliary System. Coll. Papers Mayo Clinic, 1923, vol. xiv, p. 148.
[46] Graham: *L. c.*[3]
[47] Rous and McMaster: Concentrating Activity of Gall-bladder. Jour. Exp. Med., 1921, vol. xxxiv, p. 47.
[48] Aschoff: Uber Ortho. and Pathol. der extrahepatischen gallenwege. Archiv. f. Klin. Chir., 1923, vol. cxxvi, p. 245.